UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,173	05/22/2006	Stefano Turchetta	622-95	4021

23117 7590 04/06/2009
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
MORRIS, PATRICIA L	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
04/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,173	TURCHETTA ET AL.	
	Examiner	Art Unit	
	Patricia L. Morris	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-76* is/are pending in the application.

4a) Of the above claim(s) *39-46 and 57-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-38 and 47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 34-38 and 47-56 are under consideration in this application.

Claims 39-46 and 57-76 are held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

Election/Restrictions

Applicants' election of Group I without traverse in the reply, filed January 26, 2009 is acknowledged.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34-38 and 47-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Grunenberg et. al. I (US 5,849,752).

Grunenberg et al. specifically disclose the instant compound. Note examples 1-3 of Grunenberg et al. The prior art's pharmaceutical composition comprising the instant compound would be the same as the instant compositions comprising form I, since form I would no longer exist in solution, or after granulation, compaction or tableting process, as it is well known in the art that such process(es) would lead to alteration of the crystal structure. Note, for example, Chemical & Engineering News, pages 33-34. It is well known in the art that the forms would lose their unique crystalline structure especially in solutions.

Hence, the instant compound is deemed anticipated therefrom.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-38 and 47-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Grunenberg et al. in view of Chemical & Engineering News, Feb. 2003, Brittain et al. (Polymorphism in Pharmaceutical Solids, pages 1-2, 183-226), US Pharmacopia, 1995, pp 1843-1844, Muzaffar et al. (J. of Pharmacy (Lahore) 1979, 1(1), 59-66), Jain et al. (Indian Drugs, 1986, 23 (6), Taday et al. (J of Pharm. Sci, 92 (4), April 2003, 831-838) and Concise Encyclopedia Chemistry, page 872-873 (1993).

Grunenberg et al. teach the crystal form of the instant known compound and as well as the pharmaceutical compositions. Note examples 1-3 of Grunenberg et al. Haleblian et al., Muzaffar et al., Jain et al., Britain et al. and Taday et al. teach that compounds exist as polymorphs. Chemical & Engineering News, Muzaffar et al., US Pharmacopia and Concise

Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. The prior art's pharmaceutical composition comprising the instant compound would be the same as the instant compositions comprising the form I, since the form I would no longer exist in solution, or after granulation, compaction or tableting process, as it is well known in the art that such process(es) would lead to alteration of the crystal structure. Note, for example, Chemical & Engineering News, pages 33-34. It is well known in the art that the forms would lose their unique crystalline structure especially in solutions. Jain et al. on page 316 disclosed that *"when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution".* After absorption in a physiological environment, the crystal lattice structure is lost, hence, the instant compositions are drawn to the same substance as the prior art. Hence the claimed method is deemed to be obvious therefrom because it is expected that a new crystalline form or hydrate of a known drug would treat a disease identically to the prior compound because the hydrate or crystalline form dissolves inside the body and loses its novel characteristics, i.e,. its unique lattice structure. Rowland & Tozer illustrate the process by which pharmaceutical compositions travel through the body. See page 123. This graphic shows that the drug travels into the stomach, through the gut wall, into the portal vein to the liver. The drug that withstands the liver travels through the blood to a target site where it exhibits its therapeutic function. At the target site, because the drug molecules bind to a receptor or enzyme one at a time, the crystal must be dissolved in order to bind. Silverman on page 73 pictorially illustrates molecular action of protein/substrate binding. Moreover, Jain et al. on page 316 recites that "polymorphs will be different in crystal structure but identical in the liquid or vapour states. Further, in the aqueous

phase, all physical forms are amorphous (see Ulicky). Hence, it would be excepted that the instant crystalline solvate and hydrate forms will be the same as the prior art when administered. Hence the claimed crystalline form as well as its relative selectivity of properties *vis-a-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different polymorphic forms. No unexpected or unobvious properties are noted.

Changing the form, purity or other physical characteristic of an old product does not render the new form patentable where the difference in form, purity or characteristic is inherent or rendered obvious by the prior art. In re Cofer 148 USPQ 268. Mere difference in physical property is a well known conventional variation for the same pure substance (see Brittain, p. 1-2) is prima facie obvious.

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as well as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, or was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of invention and breadth of the claims

Claims 52-56 are drawn to pharmaceutical composition comprising a compound keeping its crystalline property, whereas claims 47-51 are drawn to a method of treating bacterial infections in patients. The field of pharmaceutical composition of crystalline product is highly unpredictable and empirical.

It is well known in the art, at a given pressure and temperature only one thermodynamically stable crystalline form will exist for a given compound (see encyclopedia supra and US Pharmacopia). It is further well recognized in the art that when a crystalline form for a drug is prepared into a solid formulation, the "form" is expected to change in an unpredictable manner (Bakale et al. '646, col. 2, lines 32-34), eventually to the most thermodynamically stable one. Hence, it is expected in the art that when a crystalline form for a

drug is prepared into a solid formulation, *unless specific and* particular conditions can be described, the "form" is expected to change to the most thermodynamically stable one.

The state and skill level of the art and predictability

The state of the pharmaceutical composition containing polymorphic form art provided per ponderous of evidence that *unless specific and particular* conditions can be obtained, the formulation process would cause polymorphic forms to change.

See :

--Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form .... " And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

--Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

--Doelker et al., 2002 abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or the dosage form"

--Doelker et al. 1999 (already of record) abstract "...a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (grinding, tableting, granulations, drying) may also affect secondary properties of the drug, such as compactibility, wetttability, solvent, dissolution rate, bioavailability and even pharmacological, activity."

--Otsuka et al. p.852 ...in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process"

Taday et al. p. 831 states "Once in the desired crystalline form, the polymorphis state *may be changed* by incorrect storgage or even during tablet preparation and p. 836, figure 8, wherein compound of four form in pharmaceutical composition resulted in similar spectra, *i.e.,* form.

The pharmaceutical composition field has well recognized that stability of an active principle i.e. specific polymorphic form of a compound, has no predictability on its outcome in composition processing. It is known in the art that:

--Singhal et al. "..It should be pointed out that a major portion of any formulation effort is the choice of exipients and processes which minimize the chemical instability of the drug...." P.338, left col.

--CMU phar. Polymorph. "there are a number of examples in which polymorphic molecules change crystal structure under processing conditions while in contact with liquids or solid material. In these enviroments, it is difficult to apply standard techniques to identify the predict the transformation...." See p.1-2 para.

--US 6,627,646, col. 1-2, especially, "..from thermodynamic considerations only one polymorph will be stable;.....however, thermodynamic stability is not sufficient to ensure that the stable polymorph will always be produced.....most transformations occur in suspension and are solvent mediated.....other transformations are irreversible over a broad range of temperature:

The amount of guidance/experimentation and working examples

Claims 52-56 recite that any conventional carrier or diluent is used. Note that all liquids are non-crystalline, thus, are known to abolish crystallinity.

The specification provides no description or enablement as to how the newly acquired "form" can be prepared into a composition which can maintain the particular crystalline structure without the conventional recognized conversion to other forms i.e. amorphous form in liquid, emulsion etc. Per ponderous of evidence in the prior art indicated that for a given polymorph, *absent of any description or enablement* from the specification, does not *automatically* keeps its form in the pharmaceutical composition. Therefore, absent of description or enablement in the specification, the mere listing of a general pharmaceutical carriers does not *automatically* keeps its form in the pharmaceutical composition.

Also, note that as it has been delineated by evidence of the field, transformation of polymorph in pharmaceutical composition is not chemical stability of a crystalline form alone but its interaction with material and condition while composition is being made. Processing for composition including conventional and liquid material which are well known to abolish

crystallinity of a compound. The synthesis, isolation and characterization of a crystal, thus, provided no description or enablement that how such crystallinity, stability or physical characteristic of the isolated "form" will be incorporated and stayed in a formulation.

Further, the specification has also not described how all the crystalline form in the composition being claimed will be maintained and prevented from converting to other forms when used in the treatment of a bacterial infection. It is well recognized in the art that the compound is given to the subject in a physiological environment, *i.e.,* administered. As discussed supra, there is no description or enabling support that the instant polymorph will be in its physical form and biological activity results from the particular form instead of the solution state of the compound.

No where in the specification is a composition of "the particular XRD" of the claimed form is described or made, that is the composition contains the material having the XRD peaks recited in claims 52-56.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

In view of the per ponderous of evidence as delineated supra, it is evidenced that a crystalline drug does not automatically keeps its form in the pharmaceutical composition, thus *absent of any description or enablement* from the specification, enablement for the claimed composition and use is lacking.

Drawings

The formal drawings filed on May 22, 2006 have been accepted.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Patricia L. Morris/
Primary Examiner, Art Unit 1625

plm
March 31, 2009